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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,436	01/10/2002	Junming Le	0975.1005-018	3843

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,436	LE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-12,14,15,21,23,24 and 26-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-12,14,15,21,23,24 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 12/2/05 has been entered.

Applicant's amendment, filed 12/2/05, has been entered.
Claims 16-20, 22 and 25 have been canceled. Claims 2, 6 and 13 have been canceled previously.
Claims 1, 3-5, 7-8, 11-12, and 14-15 have been amended
Claims 26-32 have been added.

Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 4/11/05.
The rejections of record can be found in the previous Office Action, mailed 10/7/04.

3. Applicant's assertions concerning priority of the instant application have been fully considered but are not found convincing essentially for the reasons set forth herein.

Applicant's reliance upon page 58 of the instant specification as well as the disclosure of the priority application USSN 07/670,827 to support the recitation "TNF-α-mediated viral infection" is acknowledged.

However, the recitation of "TNF-α-mediated viral infection" is not readily apparent either in the pending or priority application.

It appears that applicant relies upon a generic description of TNF-α-mediated human diseases and the disclosure of "infections, including, but not limited to ... viral ... , such as HIV, ... ", to support the recitation of "TNF-α-mediated viral infection", as currently claimed.

While the cytokine TNF-α may be capable of activating certain viruses, viral infections are due to infection by viruses and are not mediated or transmitted by TNF-α.

For a more complete discussion, see the rejections under 35 USC 112, first paragraph, new matter and enablement below.

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

Further, neither the priority applications nor the instant application have provides a sufficient description of a representative number of species to represent the entire genus of "TNF-α-mediated viral infections", as currently claimed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Therefore, reliance upon the genus of "TNF-α-mediated human diseases" and the disclosure of the "viral infection, and only disclosing HIV" in a general context under the heading of TNF-related pathologies does not provide sufficient written description for "TNF-α-mediated viral infections", as currently claimed.

Also, it is noted that "wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 3, 4 and/or 5" would appear, at best, to receive a priority date back to USSN 08/192,093, filed 2/4/94 (now U.S. Patent No. 6,284,471).

Given the number of continuation-in-part applications, applicant is invited to clarify the support under 35 USC 112, first paragraph, for the priority of the instant claims in the lineage of priority documents for establishing the record for clarity.

If applicant desires priority prior to 2/21/03 for the instant claims; applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Applicant's amendment to the specification, filed 12/2/05 has obviated the previous objection under 35 U.S.C. 132 of the amendment, filed 4/11/05, because it introduced new matter into the disclosure with respect to the limitation "hepatitis".

6. Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed: "TNF-α-mediated viral infection".

Applicant's amendment, filed 12/2/05, asserts that no new matter has been added and relies upon the disclosure of page 58 of the instant specification for support of "TNF-α-mediated viral infection".

Applicant's reliance upon page 58 of the instant specification as well as the disclosure of the priority application USSN 07/670,827 to support the recitation "TNF-α-mediated viral infection" is acknowledged.

However, the recitation of "TNF-α-mediated viral infection" is not readily apparent either in the pending or in the earliest priority application.

It appears that applicant relies upon a generic description of TNF-α-mediated human diseases and the disclosure of "infections, including, but not limited to ... viral ... , such as HIV, ... ", to support the recitation of "TNF-α-mediated viral infection", as currently claimed.

While the cytokine TNF-α may be capable of activating certain viruses, viral infections are due to infection by viruses and are not mediated by TNF-α.

Therefore, reliance upon the genus of "TNF-α-mediated human diseases" and the disclosure of the "viral infection, and only disclosing HIV" in a general context under the heading of "TNF-related pathologies" does not provide sufficient written description for "TNF-α-mediated viral infections", as currently claimed.

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

Further, neither the priority applications nor the instant application have provides a sufficient description of a representative number of species to represent the entire genus of "TNF-α-mediated viral infections", as currently claimed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The specification as filed does not provide a sufficient written description or set forth the metes and bounds of this phrase. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitation", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

7. Applicant's amendments, including the Townsend Declaration under 37 CFR 1.132, have satisfied the deposit requirements under 35 USC 112, first paragraph with respect to the A2 antibody (ATCC PTA-7045).

8. Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo experimental observations of the anti-inflammatory properties of "TNF-α-specific antibodies accurately reflects the relative efficacy of the claimed therapeutic strategy to treat "TNF-α-mediated viral infections".

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

While certain viruses may be capable of activating TNF-α expression, viral infections are due to infection by viruses and are not mediated by TNF-α.
Therefore, applicant has not enabled "-mediated viral infection"

Further, it is noted that cytokines produced at early times during certain but not all viral infections with known direct antiviral functions are natural killer cell-produced interferon-gamma and tumor necrosis factor-alpha (e.g. see Tumor Necrosis Factor- α and Interferon- γ on page 1303 of Paul (ed.), Fundamental Immunology, Fourth Edition, Lippincott-Raven Publishers, Philadelphia, 1999).

Given that TNF-α can have potent anti-viral effects, there is insufficient direction and guidance as to how to "treat TNF-α-mediated viral infections" by administering "a TNF-α-inhibiting amount of an TNF-α antibody", which would block the anti-viral effects of TNF-α and, in turn, either exacerbate viral infections or not treat viral infections.

For example, Chan-Tack et al. (J. Rheumatol 33: 191-192, 2006) note that anti-TNF-α antibodies may increase susceptibility to West Nile virus by inhibiting adequate TNF-α response, leading to prolonged viremia, viral penetration into the central nervous system and disease (see entire document, including the Abstract). In addition, this Case Report indicates that clinicians should encourage patients receiving anti-TNF-α drugs to take appropriate preventive measures of the risk of severe West Nile virus disease (also, see entire document, including the Abstract).

Also, Kuwano et al. (Viral Immunology 6: 1-11, 1993) observed that enhanced lysis of influenza-infected cell by TNF-containing supernatants was inhibited by the pretreatment of the supernatant with anti-TNF antibody (see entire document, including the Abstract).

Therefore, the administration of anti-TNF-α antibodies may exacerbate viral infections rather than treat viral infections.

There is insufficient direction and guidance as to how choose which viral infections are amenable to treatment with anti-TNF-α antibodies. The claims appear to run contrary to the antiviral effects of TNF-α.

Also, given the breadth of "viral infections" and the absence of working examples, there appears to be insufficient guidance and direction as to how to how to practice the breadth of "viral infections" to be treated by administering "a TNF-α-inhibiting amount of an TNF-α antibody" to treat "any viral infection".

The specification does not teach how to extrapolate data obtained from in vitro and in vivo inhibition of certain immune or inflammatory responses with anti-TNF-α antibodies to the development of effective in vivo human therapeutic methods to treat viral infections, commensurate in scope with the claimed invention. Therefore, reliance upon the anti-inflammatory properties of anti-TNF-α antibodies does not provide for the skilled artisan to predict that treatment of viral infections or the scope of viral infections encompassed by the claimed methods would be predictable.

While applicant may assert that the claims are only directed to TNF-α-mediated viral infections and, in turn, the claims do not read on treating all viral infections, again it is noted that viral infections are caused by viruses, not cytokines such as TNF-α. Also, there is insufficient guidance and direction as to those viruses that would be considered TNF-α-mediated viral infections in the specification as filed.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 18 24 (CCPA 1970).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective anti-viral therapies with anti-TNF-α antagonist / antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting viral infections.

9. Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32 are indefinite in the recitation of "TNFα-mediated viral infection" because the metes and bounds of said "TNFα-mediated viral infection" is ill-defined and ambiguous.

As pointed out above, viruses cause viral infection, not cytokines such as TNFα.

Also, given the antiviral nature of TNFα, the metes and bounds of which viral infection fall within the scope or metes and bounds of the claimed invention is ill-defined and ambiguous.
There is insufficient objective evidence that the ordinary artisan knew of the metes and bounds of "TNFα-mediated viral infection" at the time the invention was made.

There is insufficient description of the nature and targeted "TNFα-mediated viral infections" to apprise the ordinary artisan of the metes and bounds of the claimed methods.

B) The previous rejection with respect to the recitation of "cA2" has been withdrawn in view of applicant's amended claims, filed 12/2/05.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. As noted above, the instant claims receive a priority date of the instant application USSN 10/043,436, filed 1/10/02. Therefore, the following rejections are made with the consideration that this priority date of the instant claims.

Also as noted above with respect to instant claims 7-10, it is noted that "wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 3, 4 and/or 5" would appear, at best, to receive a priority date back to USSN 08/192,093, filed 2/4/94 (now U.S. Patent No. 6,284,471).

12. Claims 1, 3-5, 7-12, 14-15, 21, 23-24 and 26-32 are rejected under 35 U.S.C. § 102(b) as being anticipated Le et al. (U.S. Patent No. 5,919,452) (see entire document).

Le et al. teach treating various pathologies, including viral infections such as HIV or AIDS dementia in humans (e.g. see columns 34-35 and 38) by administering the recombinant cA2 antibody of the instant invention (see columns 10-34 and Examples) (see entire document, including Description of the Prior art, Summary of the Invention, Detailed Description of the Preferred Embodiments and Claims. It is noted that Le et al. (U.S. Patent No.) does disclose a therapeutic regimen that is the same or nearly the same as disclosed in the instant specification (e.g. see Therapeutic Administration on columns 35-38.

13. It is noted that applicant has a number of copending applications in the instant family of applications with the use of the same A2 / cA2 TNF-specific antibodies.

Again, given the history of a number of continuations-in-part, it is not readily apparent whether the claims were subject to restriction and whether the claims are subject to double patenting rejections.

Applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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